



Martin, N. K., Vickerman, P., & Hickman, M. (2017). How to eliminate HCV infection by antiviral treatment. *Journal of Hepatology*, 67(1), 5-6. <https://doi.org/10.1016/j.jhep.2017.03.008>

Peer reviewed version

License (if available):
CC BY-NC-ND

Link to published version (if available):
[10.1016/j.jhep.2017.03.008](https://doi.org/10.1016/j.jhep.2017.03.008)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Elsevier at <https://www.sciencedirect.com/science/article/pii/S0168827817301423> . Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available: <http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Title: How to eliminate HCV infection by antiviral treatment

Authors: Natasha K Martin^{1,2}, Peter Vickerman², Matthew Hickman²

Affiliations: ¹Division of Global Public Health, University of California San Diego

²School of Social and Community Medicine, University of Bristol

Funding Acknowledgements: NKM, PV, and MH are supported by the National Institute for Drug Abuse [grant number R01 DA037773-01A1]. NKM is additionally supported by the University of California San Diego Center for AIDS Research (CFAR), a National Institute of Health (NIH) funded program [grant number P30 AI036214]. PV and MH also are supported by NIHR Health Protection Research Unit in Evaluation of Interventions.

Conflict of interest: NKM and PV have received unrestricted research grants from Gilead unrelated to this work, and NKM has received honoraria from Merck, AbbVie, and Janssen. MH has received honoraria unrelated to this work from Merck, Abbvie and Gilead.

Author contributions: NM wrote the first draft. NM, PV, and MH edited and approved the final version.

Word count: 1083

Refs: 19

The advent of new HCV treatments (Direct Acting Antivirals, DAAs) with >90% sustained viral response (SVR) rates in 8 to 12 weeks has ushered in an era of excitement about the possibility of elimination of HCV transmission. Tantalizing theoretical mathematical models predicting dramatic reductions in HCV chronic prevalence and incidence with scale-up of HCV treatment for those at risk of transmission have fueled this optimism¹. Recent reports of a substantial dramatic reduction in HCV incidence (~50% in 2 years) among HIV-infected MSM in the Netherlands after the roll-out of DAA therapy² has provided the first piece of empirical evidence that HCV treatment as prevention may be more than just a theoretical idea.

One major question is how the availability of DAAs translates in terms of numbers of individuals treated. In this issue, Zimmerman and authors describe the real-world treatment rates achieved in the DAA era in Germany, a setting where in theory all patients are eligible for treatment regardless of disease stage (Zimmerman et al. Real-world treatment for chronic hepatitis C infection in Germany. Analyses from drug prescription data, 2010 – 2015). The authors report an estimated 160,000 patients in Germany with diagnosed chronic HCV infection, and even more who are undiagnosed. Yet despite no restrictions on treatment in Germany, Zimmerman et al. estimated only 7,000 patients were treated within the statutory health insurance system (covering 85% of the German population) during 2014, and just over 20,000 in 2015, below that

which would have been expected based on the numbers of individual in need of therapy. We are not surprised that universal access to treatment alone is not sufficient for achieving rapid and comprehensive provision of DAA therapy to those in need of it.

First, improvements are needed in HCV diagnosis and assessment. As Zimmerman et al. note, no HCV screening policy exists in Germany, and studies have found 35-65% of those testing positive for HCV in general practices and emergency rooms were unaware of their status. Globally, many remain unaware of their HCV infection, including those at risk of transmission³. In settings where people who inject drugs (PWID) are a main risk group for transmission, targeted case-finding programs in addiction services, primary care, and prisons may be highly effective and cost-effective^{4,5}. Nevertheless, in many developing country settings the costs of diagnosis and confirmation of HCV infection are still prohibitively high. Additionally a lack of data surrounding the epidemiology of HCV in many country settings developed and developing makes it difficult to develop efficient targeted case-finding strategies and to establish the cascade of care (from the burden of disease to diagnosed cases, treated and cured)⁵

Second, universal access to therapy is likely required. Undoubtedly one of the most important issues facing HCV elimination is the high cost of DAA therapy, which continues to lead to prioritization of therapy in many settings. Indeed, Zimmerman et al. speculated that despite theoretical universal access to HCV treatment regardless of disease stage in Germany, physicians may have prioritized patients with advanced disease and put others on hold. Nevertheless, they note that ambiguities in the reimbursement system and fear of rejected claims may have led to a reluctance of clinicians to prescribe DAA therapy. In other settings prioritization and denial of insurance reimbursements may be a reality. European guidelines still prioritize HCV therapy for those with more advanced liver disease⁶. In the US, IDSA/AASLD guidelines no longer recommend treatment prioritization⁷, but insurers in many states continue to restrict therapy for those with less advanced disease⁸. This has important consequences for the HCV elimination agenda. Although prioritization of individuals with more severe liver disease may be an economic way of preventing end-stage liver disease and HCV-related mortality, it may work at odds to the prevention agenda. For example, PWID tend to be younger with less advanced liver disease and therefore strategies which target more severe liver disease may have little to no impact on the epidemic. Indeed, mathematical modeling in the UK showed that current prioritization of therapy to individuals with F3 or cirrhosis would have virtually no effect on HCV incidence among PWID⁹. However, analyses have shown that in many settings with low-moderate HCV prevalence among PWID it is more cost-effective to prioritize early therapy for individuals at risk of transmission due to substantial prevention benefits¹⁰. Still, concerns about costs of therapy and potential costs of retreatment of reinfections persist. Ongoing studies will shed light on the risk of reinfection in the DAA era, but studies in the IFN-era consistently show that the risk of reinfection among PWID after SVR is relatively low^{11,12}. Nevertheless, as observed in the US, Medicaid restrictions based on drug use history⁸ (counter to IDSA/AASLD guidelines⁷) will hamper

efforts to deliver HCV treatment to those at risk of transmission in order to prevent new infections.

Third, once access is ensured, HCV treatment needs to be scaled-up, in particular to those at risk of transmission. Unfortunately, several barriers continue to thwart the scale-up of HCV treatment for these populations, particularly PWID. Studies have indicated that PWID are willing to undergo HCV therapy¹³, yet many who are diagnosed remain untreated. Provider concerns surrounding potential poor treatment outcomes among PWID persist, despite clinical trial evidence that DAA treatment outcomes among PWID are comparable to the broader population^{14,15}. Additionally, established programs have been successful at treating HCV among PWID even in the IFN-based era; the most effective programs are built on existing infrastructure for drug user health such as addiction clinics, community health centers, and prisons.

Fourth, HCV treatment needs to be combined with prevention scale-up to enhance impact, reduce reinfection, and ensure stable reductions in transmission occur. Harm reduction intervention such as opiate substitution therapy and needle and syringe programs are effective at reducing an individuals' risk of HCV acquisition, particularly in combination^{16,17}, and are crucial for enabling any treatment intervention to effectively treat current PWID. Combination HCV treatment and harm reduction strategies can potentially act synergistically to reduce HCV incidence¹⁸, as well as prevent reinfection post treatment. However, across the globe the coverage and quality of harm reduction service provision is often low¹⁹. In settings with differing modes of transmission other prevention interventions are likely required, such as efficient blood screening, effective sterilization of medical equipment, education of unofficial health care providers, and initiatives to prevent mother-to-child transmission and between men who have sex with men.

Overall, the promise of HCV treatment as prevention is enormous, and universal access like in Germany is an important necessary, but as Zimmerman et al demonstrate not always sufficient, first step.

Reference

1. Martin NK, Vickerman P, Dore GJ, Hickman M. The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): the use of direct-acting antivirals as treatment for prevention. *Current Opinion in HIV and AIDS*. 2015;10(5):374-380.
2. Boerekamps A, van den Berk G, Lauw F, et al. SUBSTANTIAL DECLINE IN ACUTE HCV INFECTIONS AMONG DUTCH HIV+MSM AFTER DAA ROLL OUT. Abstract 137LB. CROI 2017; February 13-16, 2017, 2017; Seattle, Washington.
3. Dore GJ, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). *Journal of Viral Hepatitis*. 2014;21:1-4.

4. Martin NK, Hickman M, Miners A, Hutchinson SJ, Taylor A, Vickerman P. Cost-effectiveness of increasing HCV case-finding for people who inject drugs in specialist addiction services and prisons. *BMJ*. 2013.
5. Martin NK, Vickerman P, Brew IF, et al. Is increased hepatitis C virus case-finding combined with current or 8-week to 12-week direct-acting antiviral therapy cost-effective in UK prisons? A prevention benefit analysis. *Hepatology*. 2016;63(6):1796-1808.
6. European Association for the Study of the Liver. EASL Recommendations on Treatment of Hepatitis C 2016. 2016;<http://www.easl.eu/medias/cpg/HCV2016/Summary.pdf> (Accessed Feb 27, 2017).
7. AASLD/IDSA. *Recommendations for Testing, Managing, and Treating Hepatitis C* <http://www.hcvguidelines.org/fullreport> (Accessed Feb 27 2017). 2017.
8. National Viral Hepatitis Roundtable. *Hepatitis C: The State of Medicaid Access* (http://www.chlpi.org/wp-content/uploads/2013/12/HCV-Report-Card-National-Summary_FINAL.pdf) Accessed Feb 27, 2017. 2016.
9. Harris RJ, Martin NK, Rand E, et al. New treatments for hepatitis C virus (HCV): scope for preventing liver disease and HCV transmission in England. *Journal of Viral Hepatitis*. 2016;doi: 10.1111/jvh.12529.
10. Martin NK, Vickerman P, Dore GJ, et al. How should HCV treatment be prioritized in the direct-acting antiviral era? An economic evaluation including population prevention benefits. *Journal of Hepatology*. 2016;DOI: 10.1016/j.jhep.2016.1002.1007.
11. Aspinall A, Corson S, Doyle J, et al. Treatment of hepatitis C virus among people who are actively injecting drugs: a systematic review and meta-analysis. *Clinical Infectious Diseases*. 2013;57(Suppl 2):S80-89.
12. Midgard H, Weir A, Palmateer N, et al. HCV epidemiology in high-risk groups and the risk of reinfection. *Journal of Hepatology*. 65(1):S33-S45.
13. Alavi M, Micallef M, Fortier E, et al. Effect of treatment willingness on specialist assessment and treatment uptake for hepatitis C virus infection among people who use drugs: the ETHOS study. *Journal of Viral Hepatitis*. 2015;22(11):914-925.
14. Dore GJ, Altice F, Litwin AH, et al. Elbasvir–grazoprevir to treat hepatitis c virus infection in persons receiving opioid agonist therapy: A randomized trial. *Annals of Internal Medicine*. 2016;165(9):625-634.
15. Grebely J, Mauss S, Brown A, et al. Efficacy and Safety of Ledipasvir/Sofosbuvir With and Without Ribavirin in Patients With Chronic HCV Genotype 1 Infection Receiving Opioid Substitution Therapy: Analysis of Phase 3 ION Trials. *Clinical Infectious Diseases*. 2016;63(11):1405-1411.
16. Turner K, Hutchinson S, Craine N, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of Hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction* 2011;106(11):1978-1988.
17. Van Den Berg D, Smit D, Van Brussel G, Coutinho R, Prins M, Amsterdam C. Full participation in harm reduction programmes is associated with decreased risk for human immunodeficiency virus and hepatitis C virus:

- evidence from the Amsterdam Cohort Studies among drug users. *Addiction*. 2007;102(9):1454-1462.
- 18.** Martin NK, Hickman M, Hutchinson SJ, Goldberg DJ, Vickerman P. Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 8/2013 2013;57 Suppl 2:S39-S45.
- 19.** Harm Reduction International. The Global State of Harm Reduction 2016. https://http://www.hri.global/files/2016/11/14/GSHR2016_14nov.pdf. 2016.